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SYSTEMATIC REVIEW WITH META-ANALYSIS

Tranexamic acid as treatment for acute gastrointestinal bleeding: A comprehensive systematic review and meta-analysis

Ernesto Calderon Martinez[1] · Gabriela D Briceño Silva[2] · Camila Sanchez Cruz[3] · Nathnael Abera Woldehana[4] · Yash Shah[5] · Dushyant Singh Dahiya[6] · Manesh Kumar Gangwani[7] · Saurabh Chandan[8] · Fides Myles C. Caliwag[9] · Rodrigo Sebastian Maldonado[10] · Rubeliz Bolivar-Barrios[11] · Ada Motino[12] · Rashmi Advani[13]

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Abstract

Introduction Gastrointestinal (GI) bleeding is a common and potentially life-threatening medical emergency. Despite advancements in therapy, mortality rates associated with GI bleeding remain high (2.4% to 11%). Tranexamic acid (TXA) has been proposed as a treatment. However, the HALT-IT trial questioned its efficacy and safety, showing no significant reduction in death and potential thrombotic complications. This meta-analysis aims to evaluate the effectiveness and safety of TXA in treating acute GI bleeding.

Methods This systematic review and meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. In October 2024 a comprehensive literature search was conducted using relevant MeSh terms and keywords in 11 databases. We included patients with acute GI bleeding treated with TXA and compared it with either a placebo or standard treatment. Outcomes such as mortality, need for blood transfusion, surgery and thrombotic events were studied.

Results The search identified 6810 articles. After screening, 23 studies were included, encompassing 2,061,231 participants. Our meta-analysis demonstrated that TXA significantly reduced rebleeding rates overall (RR: 0.81, 95% CI: 0.87-0.97). This effect was even more pronounced in studies with a lower risk of bias. Additionally, TXA use was associated with a mortality reduction when administered through both oral and intravenous routes (RR: 0.56, 95% CI: 0.35-0.89) and in cases of upper GI bleeding (RR: 0.72, 95% CI: 0.59-0.87). However, TXA was linked to a significant increase in mortality in patients with lower GI bleeding (RR: 1.67, 95% CI: 1.44-1.93) and overall reduction when only randomized controlled trials (RCTs) were included (RR:0.83, 95% CI; 0.70 to 0,97, I2=0%). Other variables, such as the overall need for blood transfusions (RR: 1.03, 95% CI: 0.80-1.32), thrombotic events (RR: 1.30, 95% CI: 0.75-2.23) and the need for surgical intervention (RR: 0.78, 95% CI: 0.57-1.09), did not reach statistical significance. However, when considering only low risk of bias studies the need for surgical interventions was significantly reduced (RR: 0.85, 95% CI: 0.75 to 0.97, I2=0%).

✉ Ernesto Calderon Martinez
ernestocalderon.mtz@gmail.com

1 The University of Texas Science Medical Center at Houston, Houston, Texas, USA

2 Universidad de Oriente, Barcelona, Venezuela

3 Universidad Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico

4 Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

5 Department of Internal Medicine, Trinity Health Oakland, Pontiac, MI, USA

6 Division of Gastroenterology, Hepatology and Motility, School of Medicine, The University of Kansas, Kansas City, KS, USA

7 Division of Gastroenterology and Hepatology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

8 Division of Gastroenterology and Hepatology, AdventHealth Orland, Orlando, FL, USA

9 Ateneo School of Medicine and Public Health, Pasig City, Philippines

10 Universidad Nacional de Cordoba (UNC), Cordoba, Argentina

11 Universidad de Oriente, Barcelona, Venezuela

12 Universidad Católica de Honduras, Tegucigalpa, Honduras

13 Department of Gastroenterology and Hepatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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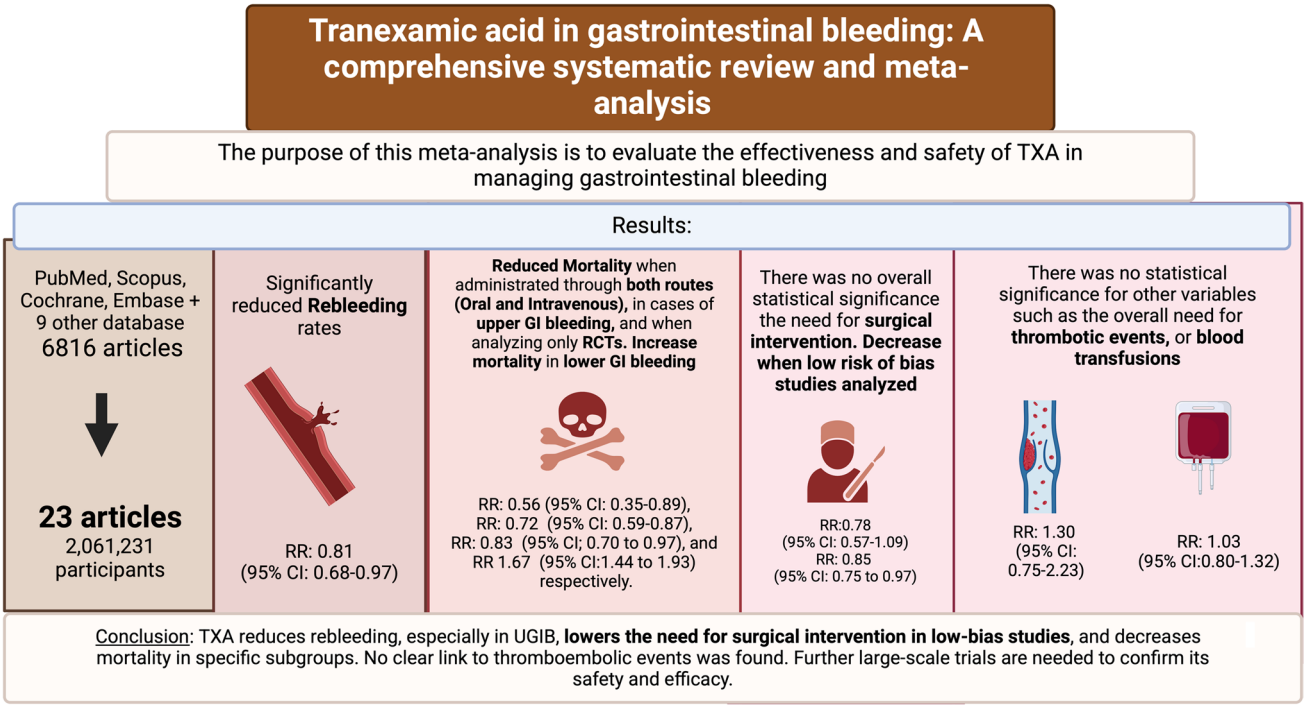
Conclusions Our findings suggest that TXA significantly reduces rebleeding in patients, particularly in upper gastrointestinal bleeding (UGIB) and reduces need for surgical intervention when excluding high risk of bias studies. The findings also demonstrated a significant reduction in mortality, particularly in certain sub-groups. There was no definitive evidence that its use is associated with thromboembolictic events. These results highlight the potential benefit of TXA without dismissing the need for cautious interpretation and individualized patient management when considering TXA for GI bleeding.

Graphical Abstract


Tranexamic acid in gastrointestinal bleeding: A comprehensive systematic review and meta-analysis
The purpose of this meta-analysis is to evaluate the effectiveness and safety of TXA in managing gastrointestinal bleeding
Results:
PubMed, Scopus, Cochrane, Embase + 9 other database
6816 articles
23 articles
2,061,231 participants
Significantly reduced Rebleeding rates
RR: 0.81 (95% CI: 0.68-0.97)
Reduced Mortality when administrated through both routes (Oral and Intravenous), in cases of upper GI bleeding, and when analyzing only RCTs. Increase mortality in lower GI bleeding
RR: 0.56 (95% CI: 0.35-0.89), RR: 0.72 (95% CI: 0.59-0.87), RR: 0.83 (95% CI; 0.70 to 0.97), and RR 1.67 (95% CI:1.44 to 1.93) respectively.
There was no overall statistical significance the need for surgical intervention. Decrease when low risk of bias studies analyzed
RR:0.78 (95% CI: 0.57-1.09) RR: 0.85 (95% CI: 0.75 to 0.97)
There was no statistical significance for other variables such as the overall need for thrombotic events, or blood transfusions
RR: 1.30 (95% CI: 0.75-2.23)
RR: 1.03 (95% CI:0.80-1.32)
Conclusion: TXA reduces rebleeding, especially in UGIB, lowers the need for surgical intervention in low-bias studies, and decreases mortality in specific subgroups. No clear link to thromboembolic events was found. Further large-scale trials are needed to confirm its safety and efficacy.

Keywords Antifibrinolytics · Gastrointestinal bleeding · Tranexamic acid · Thrombotic events · *RR* relative risk · *GI* gastrointestinal · *RCTs* randomized controlled trials

Introduction

Gastrointestinal (GI) bleeding is a common and potentially life-threatening medical emergency, accounting for many hospitalizations worldwide [1]. Despite advancements in therapies and management, mortality rates associated with GI bleeding remain high, ranging from 2.4% to 11% [2–4]. The most common causes for upper GI bleeding (UGIB) include peptic ulcer disease, esophagitis and gastritis (30, 12.2 and 10 cases per 100,000 population, respectively). The leading causes for lower GI bleeding (LGIB) are diverticular disease (30%), hemorrhoids (14%) and ischemic colitis (12%) [2–4]. The mortality rate for UGIB ranges from 8% to 10% in de novo hospitalizations to 26% in hospitalized patients [4]. The mortality rate in LGIB is comparatively lower (3.4% to 8.8%) and deaths due to severe bleeding are <1% (4). UGIB has decreased recently from 66 cases per 100,000 population in 1987 to 45 cases per 100,000 population in 2016 due to the widespread use of proton pump inhibitors (PPI) and the declining prevalence of *Helicobacter pylori* infection [3, 5]. However, LGIB has increased from six cases per 100,000 population in 1987 to 45 cases per 100,00 population in 2016, and the rise is particularly noted among the elderly [4, 5].

Tranexamic acid (TXA), an antifibrinolytic agent that inhibits the breakdown of blood clots, has been proposed as a potential treatment for GI bleeding. TXA reduces bleeding and mortality in settings such as trauma, postpartum hemorrhage and surgery [6]. However, the analyses cited to propose TXA for GI bleeding had significant methodological limitations. For example, the HALT-IT trial, a large, international, multicenter, randomized controlled trial (RCT), has called into question the efficacy and safety of TXA in managing GI bleeding [7]. It included 12,009 patients with acute or lower GI bleeding and found no significant reduction in death with TXA compared to placebo.

Furthermore, this trial raised concerns about the potential for increased adverse events with TXA, particularly thrombotic complications, noting a 1.4% incidence of events in the TXA group vs. 1.2% in the control group [7]. A subsequent meta-analysis that included data from the HALT-IT trial and three other large trials of TXA in acute severe bleeding found no evidence of heterogeneity in the effect of TXA on mortality across different bleeding sites, but also warned against over-optimism in the interpretation of the potential benefits of TXA, considering its risks [8].

Given the conflicting evidence and potential for harm, there is a pressing need for an updated, rigorous and comprehensive meta-analysis, including more databases and focusing on key outcomes, to clarify the role and assess the efficacy and safety of TXA in managing GI bleeding.

Methodology

The present systematic review (SR) followed the recommendations and criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [9]. The protocol was pre-registered at the International Prospective Register of Systematic Reviews (PROSPERO) with identifier code CRD42024532158.

Types of study

We systematically reviewed relevant studies published from database inception to October 2024, available in English and Spanish. We meticulously screened and analyzed cohorts of randomized controlled trials (RCTs) and case-control studies to include the highest quality studies. We excluded case series, cross-sectional studies, dissertations, book chapters, protocol articles, reviews, news articles and conference abstracts. Furthermore, we excluded studies that did not clearly describe their operationalizations, were duplicated and/or where we could not obtain needed additional data or receive a response from the original author via email.

Types of participants

This study uses specific participant selection criteria, including patients of all genders and ages with acute GI bleeding, defined as GI bleeding during the first 24-48 hours. Exclusion criteria include studies that do not specifically involve patients with acute GI bleeding. The study aims to include diverse participants to understand the intervention fully.

Type of intervention and comparator

The intervention of interest is TXA, administered to patients with acute GI bleeding, compared to a placebo or standard treatment for this condition.

Outcomes

The outcomes to be measured include studies that report relevant outcomes, specifically, the effectiveness of TXA, the need for blood transfusion, transfusion volume, need for surgery, need for endoscopy, rebleeding, length of stay in the hospital, mortality rates and complications including thrombotic events such as cerebrovascular accidents (CVA), myocardial infarctions (MI), deep vein thrombosis (DVT) and pulmonary embolism (PE). We excluded studies that did not report these relevant outcomes.

Search strategy

In October 2024, a thorough and systematic literature search was conducted in the following electronic databases: PubMed, International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, Web of Science, Google Scholar, Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Library, EMBASE, Scopus, Latin America and the Caribbean Literature on Health Sciences (LILACS) and China National Knowledge Infrastructure (CNKI).

The search strategy was developed by selecting relevant Medical Subject Headings (MeSH) terms and keywords related to TXA, GI bleeding and study design. Boolean operators (AND, OR) were used to optimize search results. Each database's search strategy was customized to ensure comprehensive coverage (Supplementary Tables 3-13).

Selection of studies

All references were exported to Rayyan [10] and duplicates were removed. Two authors independently completed the eligibility assessment, first by title and abstract analysis, followed by a full-text assessment. In disagreements between reviewers, a third reviewer helped reach a consensus.

Data extraction

Two independent reviewers performed the data extraction and disagreements were resolved by consensus; when multiple overlapping reports from the same study were identified, the information from the one containing the most relevant information or the first published report was included. The extracted parameters included type of study, population characteristics such as age and specific disease (type of

bleeding – upper/lower), sample size, number of cases, number of control cases, specific intervention details such as dose and administration route, variceal vs. non-variceal bleeding and study results covering need for transfusion, surgery, endoscopy, the volume of transfusion, hospital length of stay, rebleeding rates, adverse events and mortality. We combined the arms within each relevant category (i.e. intervention or control) to create a single pairwise comparison for studies with multiple intervention or control arms. This approach followed the recommendations from the Cochrane Handbook to avoid double-counting participants. The combination of arms was done by summing up the number of participants and events in each relevant group [11].

Statistical analysis

A meta-analysis was performed using R version 3.4.3 (R Core Team) [12]. The pooled effect of the outcomes was examined using a random-effects meta-analysis (DerSimonian-Laird approach) [11]. Whenever the number of studies reporting an outcome of interest was insufficient, only a qualitative analysis of the results was performed. Effect sizes were expressed as Relative Risk (RR) or mean difference (MD) with 95% confidence interval. The I2 statistic assessed heterogeneity and the following cut-off values were used for interpretation: <25, 25–50 and > 50% were considered small, medium and significant heterogeneity, respectively. For all outcomes, sensitivity analyses according to the leave-one-out method were performed to determine the influence of individual studies on the overall effect. Egger's regression test examined publication bias when 10 or more reports with the same outcome were available. Whenever feasible, we conducted sub-group analyses for outcomes based on study type, year, country and follow-up duration. Additionally, we examined the dose of TXA administered on the first day, the administration route, the type of bleeding (variceal or non-variceal) and whether bleeding originated from the upper GI tract, lower GI tract or both. It is important to note that TXA was the specific intervention in all studies. The sub-groups were considered to assess the potential impact of TXA treatment on any of the outcomes for each sub-group.

Risk of bias assessment

To assess the quality of studies included in the present review, we applied two different tools: the Cochrane Risk of Bias 2.0 Tool for randomized controlled trials (RCTs) [13] and the Newcastle-Ottawa scale (NOS) for assessing the quality of cohorts and Case Controls [14]. Two independent reviewers evaluated the risk of bias in each study, considering the specific criteria and guidelines. A third blinded reviewer resolved the discrepancies between the reviewers. The risk-of-bias analysis summary for RCTs has been depicted using the risk-of-bias visualization (robes) package [15]

Results

Study identification and selection

Total 6810 possible articles were found across the 11 databases. After eliminating 1650 duplicate articles, titles and abstracts of 5160 articles were screened. From these articles, 5082 were removed from the screening process and one was marked as ineligible by automation tools. Total 77 publications were selected for full-text screening. After determining the eligibility and quality of the full-text publications, the selection was narrowed to 17 articles. We also included six additional articles from previous meta-analyses, for 23 included in the present review. The PRISMA flow chart (Fig. 1) depicts the study selection procedure.

12,009Synthesis of results

The 23 included studies consisted of 16 RCTs [7, 16–29] and seven observational studies [30–36], encompassing 2,061,231 participants. These studies were conducted in various regions, including Sweden (21.7%), Iran (17.3%), the UK (17.3 %) and Australia (8.6 %), among other countries. They were published between 1973 and 2024. The sample sizes of the studies ranged from 20 to 1.9 million patients.

While the results of the selected publications varied, a majority saw improved outcomes with TXA compared to placebo or standard treatment. Seventeen of the selected publications (74%) saw improvement in at least one parameter, such as bleeding, re-bleeding rates, mortality and/or the need for endoscopy, surgery and blood transfusions [17–20, 22–31, 33, 35, 37]. The remaining six articles (26%) saw either increased complications, no clinical benefit or no significant difference. Detailed characteristics of the included studies are summarized in Table 1. Receiving high-dose 24-hour TXA infusion did not reduce deaths from GIB but increased the risk of venous thromboembolic events and seizures compared to placebo.

Several studies reported adverse outcomes in the form of thrombotic events. Seven studies (30.4%) showed a higher rate of these events in the TXA group than the placebo, while five studies (21.7%) demonstrated more adverse events in the control group. Additionally, from the eight studies reporting the need for endoscopic intervention, the TXA

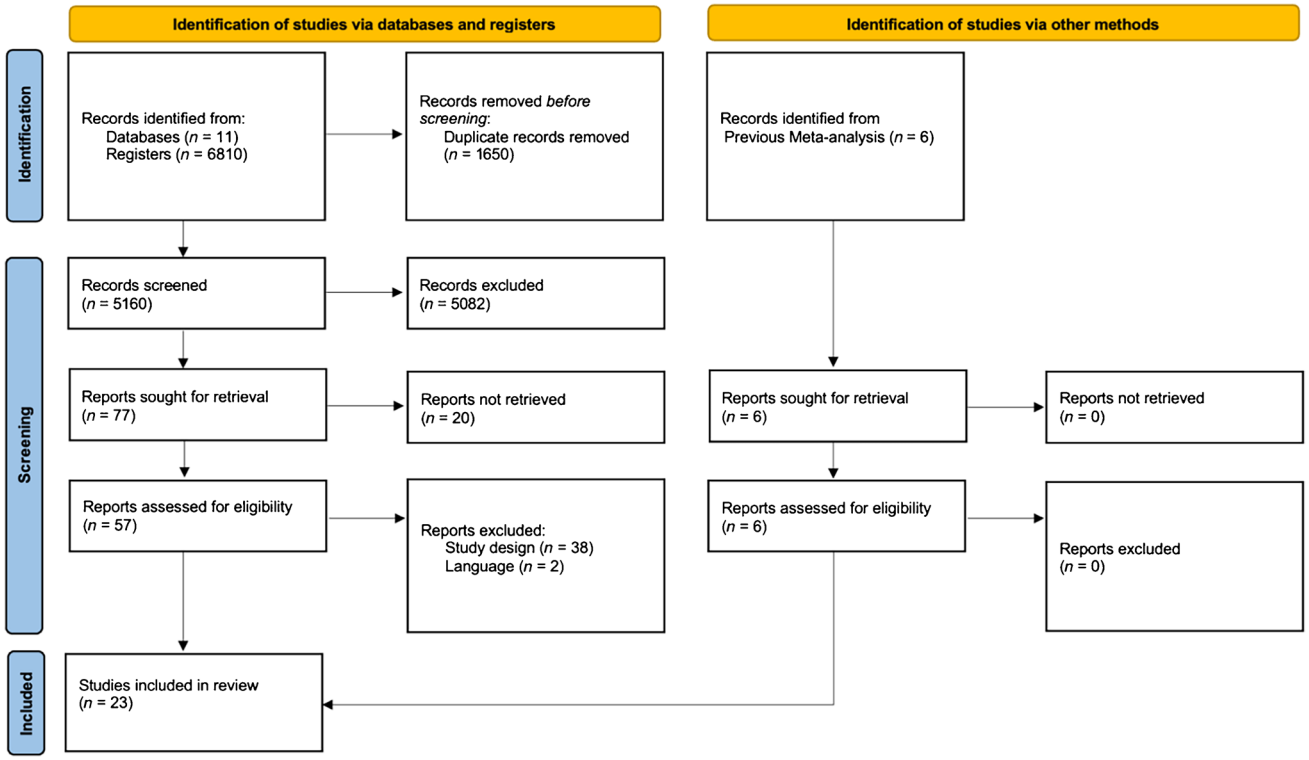


Fig. 1 *S*ummary of the risk of bias analysis of the included studies, demonstrating low risk (green), some concerns (yellow) and high risk for bias (red). Created using risk-of-bias visualization (robvis) package [15]

group exhibited a reduced need for endoscopy in four studies (50%).

The risk of bias assessment using Cochrane's Risk of Bias 2.0 tool for RCTs, shows the results of the 15 included studies depicted in Fig. 2 in three colors: green for low risk, yellow for some concerns and red for high risk. Our selection showed that most of our publications, six of them (40%), resulted in low risk, five (33.3%) showed some concerns and the four remaining articles (26.6%) showed a high risk of bias. For the prospective and retrospective studies using the NOS, our selection showed that six (75%) of the studies were of Good Quality, while the remaining two (25%) were of Fair Quality (Table 2).

Transfusion rate

This analysis included 13 studies, encompassing 92,764 participants (37,765 in the TXA group and 54,999 in the placebo group) and recorded 29,517 transfusion events. The random-effects model showed a RR of 1.03 (95% CI: 0.80 to 1.32, $p = 0.82$, I2=97%) (Fig. 3A). The funnel plot showed asymmetry, but Egger's test ($p = 0.46$) did not indicate significant publication bias. The asymmetry may be due to heterogeneity or study design differences rather than bias (Fig. 3B).

Sub-group and sensitivity analyses

Sub-group analyses identified significant between-group differences for study year ($p < 0.01$), country ($p < 0.01$), administration route ($p < 0.01$) and type of study ($p < 0.01$). However, many significant findings were based on single-study sub-groups, limiting their reliability and increasing the risk of bias. For example, in the case of year and type of study sub-groups, meta-regression analysis was performed to assess the effect of publication year on the outcome and the test of moderators showed no significant association ($p = 0.46$). Studies from Iran showed the highest heterogeneity; none of the sub-groups for the administration route showed a significant effect in the analysis despite showing differences between groups. Other sub-group analyses showed no significant differences, suggesting these factors did not modify the overall effect. Sensitivity and leave-one-out analyses did not reveal any particular study that influenced the overall result (Supplementary Tables 12 and 13).

Thrombotic events

This analysis included 12 studies, comprising 1,964,475 participants (17,034 in the TXA group and 1,947,441 in the placebo group) and reported 109,890 thrombotic events. The random effects model yielded an RR of 1.30 (95% CI:

Table 1 Summary of results for included studies

Author	Year	Type of study	Specific intervention	Sample size	Disease	Ca	Co	Conclusion
Roberts et al. [41]	2021	Multicenter, randomized, placebo-controlled trial	TXA.1g loading dose over 10 min, then 3g maintenance dose over 24 hours total)	12,009	GIB	5994	6015	Receiving high-dose 24-hour TXA infusion did not reduce deaths from GIB but increased the risk of venous thromboembolic events and seizures compared to placebo.
Karadaş et al. [16]	2020	Single center, prospective, double-blind, placebo-controlled, RT	TXA.locally administered via nasogastric route using 2000 mg of 5% TXA in 100 mL of isotonic saline solution	157	UGIB	78	79	A single topical dose of TXA did not significantly improve outcomes such as rebleeding, mortality or need for surgical intervention compared to placebo in patients with UGIB.
Tavakoli et al. [17]	2018	Double-blinded, RCT	Ca: TXA. 1 g/q6h intravenous Co: placebo. (Sodium chloride 0.9%)	410	GIB	138	139	Intravenous and topical TXA reduced the need for urgent endoscopy compared to placebo in patients with UGIB but did not significantly affect other outcomes such as rebleeding or mortality.
Bashiri et al. [18]	2021	Double-blinded RCT	TXA IV loading dose of 1 g, then maintenance infusion of 1 g over 8 hours	70	GIB	35	35	Intravenous TXA reduced rates of rebleeding but had no significant effect on mortality compared to placebo in patients with massive UGIB.

Table 1 (continued)

Author	Year	Type of study	Specific intervention	Sample size	Disease	Ca	Co	Conclusion
Sedaghat et al. [19]	2023	Double-blinded, RCT	TXA (IV 500 mg loading dose, then 1 g infusion over 8 hours)	86	UGIB	43	43	Intravenous TXA reduced rebleeding rates but not mortality compared to placebo in patients with massive UGIB. One transient ischemic attack occurred in the TXA group.
Saidi et al. [20]	2017	Prospective, double-blind placebo-controlled RT	Intra-gastric TXA (1g) followed by 1g four times daily	131	UGIB	67	64	Topical TXA significantly reduced rebleeding and mortality rates compared to placebo in patients with UGIB without increasing the risk of thrombotic events.
Smith et al. [21]	2018	Single center, placebo-controlled, patient and observer-blinded, RCT	Oral TXA 1 g, followed by 1 g four times daily for LGIB	96	LGIB	49	47	No significant differences were found between oral TXA and placebo regarding transfusion requirements, need for surgery, length of hospital stay or mortality rates.
Kumar et al. [22]	2024	Single center, RCT	IV TXA 1 g loading dose, followed by 3 g over 24 hours in patients with cirrhosis and UGIB	600	UGIB	300	300	The findings on patients with cirrhosis and UGIB indicated that IV TXA reduced rebleeding but not mortality compared to placebo. One transient ischemic attack occurred in the TXA group. All patients received PPI.

Table 1 (continued)

Author	Year	Type of study	Specific intervention	Sample size	Disease	Ca	Co	Conclusion
Hawkey et al. [23]	2001	Randomized double-blind, double-dummy, parallel-group comparison of placebo-trial	Oral TXA. 2g, followed by 1g four times daily	414	UGIB	106	103	Oral TXA reduced the presence of blood in the stomach at endoscopy in patients with UGBI. Still, it did not significantly affect rebleeding rates, need for surgery or mortality compared to placebo.
Miyamoto et al. [30]	2021	Retrospective observational cohort study	IV TXA	78,291	LGIB	30,526	47,765	Receiving TXA was linked to a notable decrease in severe bleeding, blood transfusion rates and hospital stay duration.A non-significant increase of mortality was reported
Bai et al. [31]	2024	Retrospective cohort study	IV TXA	168	UGIB	83	85	The administration of TXA injection for GI hemorrhage led to notably improved clinical outcomes in the TXA group compared to the control group. This study's results were limited by small sample size.
Scherdin et al. [32]	2021	Retrospective cohort study	TXA treatment (not specified)	387	UGIB	139	247	This study found no data to support treating bleeding ulcers with TXA. No significant difference existed between patients using TXA and those in the control group.

Table 1 (continued)

Author	Year	Type of study	Specific intervention	Sample size	Disease	Ca	Co	Conclusion
Ting et al. [33]	2022	Retrospective cohort study	TXA treatment (not specified)	14,686	GIB	9513	5173	Early administration of TXA was correlated with lower mortality rates. Compared to late treatment, no increase in thromboembolic events among patients with GI bleeding was found.
Reeden [34]	2017	Retrospective cohort study	TXA treatment (not specified)	101	UGIB	57	44	This study suggested that TXA did not result in favorable outcomes for patients with bleeding ulcers.
Chertoff et al. [35]	2017	Retrospective cohort study	TXA treatment (not specified)	1819	UGIB	16	1813	The hypothesis that TXA in UGIB is underutilized was confirmed. The data supported the fact that the utilization rate of TXA for UGIB did not differ between medical and surgical intensivists.
Fowler et al. [36]	2024	Retrospective cohort study	TXA treatment (not specified)	194,9702	UGIB	9644	194,0058	There is a significant association between the administration of TXA in UGIB patients and the development of both venous and arterial thromboembolic events.

Table 1 (continued)

Author	Year	Type of study	Specific intervention	Sample size	Disease	Ca	Co	Conclusion
Sabovic et al. [37]	2003	Pilot, non-randomized trial	TXA in a dosage of 20 mg IV, followed for the next four weeks by 10 mg/kg/48 hours orally)	20	UGIB	N/A	–	This study observed significant efficacy of TXA in all endpoints, suggesting that this drug should be beneficial as an adjunctive treatment to standard management of major UGIB.
Cormack et al. [24]	1973	Single-center, RCT	Oral TXA. 1.5 g every 8 hours for seven days.	150	UGIB	76	74	This study showed that treatment with TXA was more effective for bleeding distal to the gastroesophageal junction, likely due to acute superficial gastric erosions. It may reduce transfusion needs in these cases.
Biggs et al. [25]	1976	Single-center, RCT	IV TXA. Oral TXA	200	UGIB	103	97	This study showed that TXA can reduce bleeding in the upper gastrointestinal tract, leading to fewer surgeries.
Engqvist et al. [26]	1979	Single-center, RCT	IV TXA. Oral TXA	149	UGIB	76	73	The study showed that the tranexamic acid group required fewer blood transfusions on Day 2. There was also a reduction in surgeries in this group, though the difference was not statistically significant.

Table 1 (continued)

Author	Year	Type of study	Specific intervention	Sample size	Disease	Ca	Co	Conclusion
Bergqvist et al. [28]	1980	Single-center, RCT	TXA. administered via nasogastric route	43	UGIB	21	22	The study concluded that fibrinolytic inhibition had a small but significant effect on minor UGIB. It showed no impact on transfusion needs or surgery rates but observed a slight reduction in mortality and delayed death.
Barer et al. [27]	1983	Single-center,RCT	IV TXA. Oral TXA	516	UGIB	256	260	This study showed that TXA significantly reduced mortality. However, this reduction did not correspond to a decrease in hemorrhage severity or frequency or the number of surgeries needed to stop further bleeding.
Von Holstein et al. [29]	1987	Single-center, RCT	IV TXA. Oral TXA	154	UGIB	72	82	This study found that TXA significantly reduced the blood transfusion requirements and number of emergency operations needed in patients with UGIB.

TXA Tranexamic acid, *GIB* gastrointestinal bleeding, *RT* randomized trial, *UGIB* upper gastrointestinal bleeding, *RCT* randomized controlled trial, *LGIB* lower gastrointestinal bleeding, *PPI* proton pump inhibitors, *GI* gastrointestinal

Table 2 The Newcastle-Ottawa scale (NOS)-based results for observational studies

Author, Year	Study Design	Selection	Com-parabil-ity	Outcome/ Exposure	Total	Subjective evaluation
Miyamoto et al. 2021 [30]	Case-Control	2	2	2	6	Fair Quality
Bai. 2024 [31]	Case-Control	4	1	3	8	Good Quality
Scherdin et al. 2021 [32]	Cohort	4	1	2	7	Good Quality
Ting et al. 2022 [33]	Cohort	4	1	2	7	Good Quality
Redeen 2017 [34]	Cohort	4	1	2	7	Good Quality
Chertoff et al. 2017 [35]	Cohort	2	2	2	6	Fair Quality
Fowler et al. 2024 [36]	Cohort	4	2	2	7	Good Quality
Sabovic et al. 2003 [37]	Cohort	3	3	3	7	Good Quality

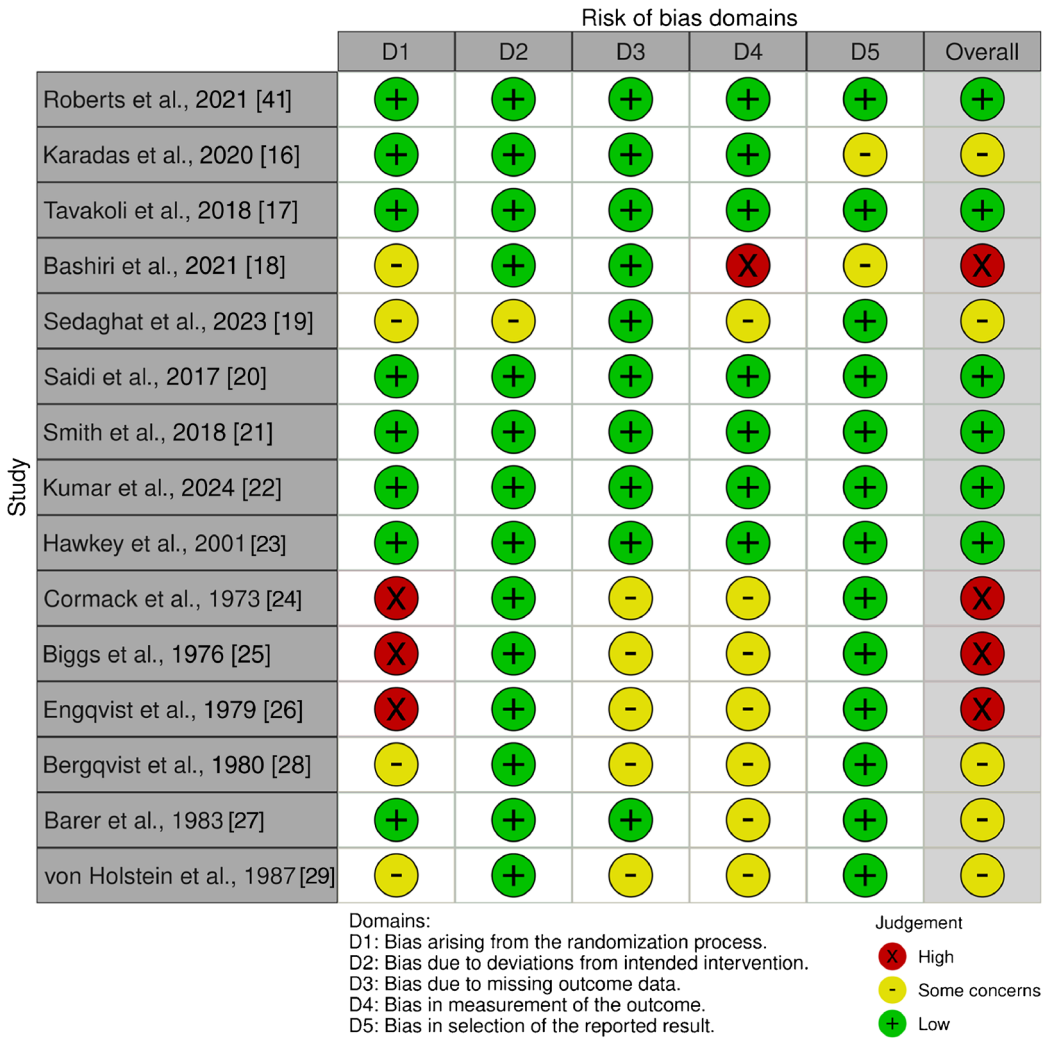


Fig. 2 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart. A summary of the process of selecting studies is included in this review

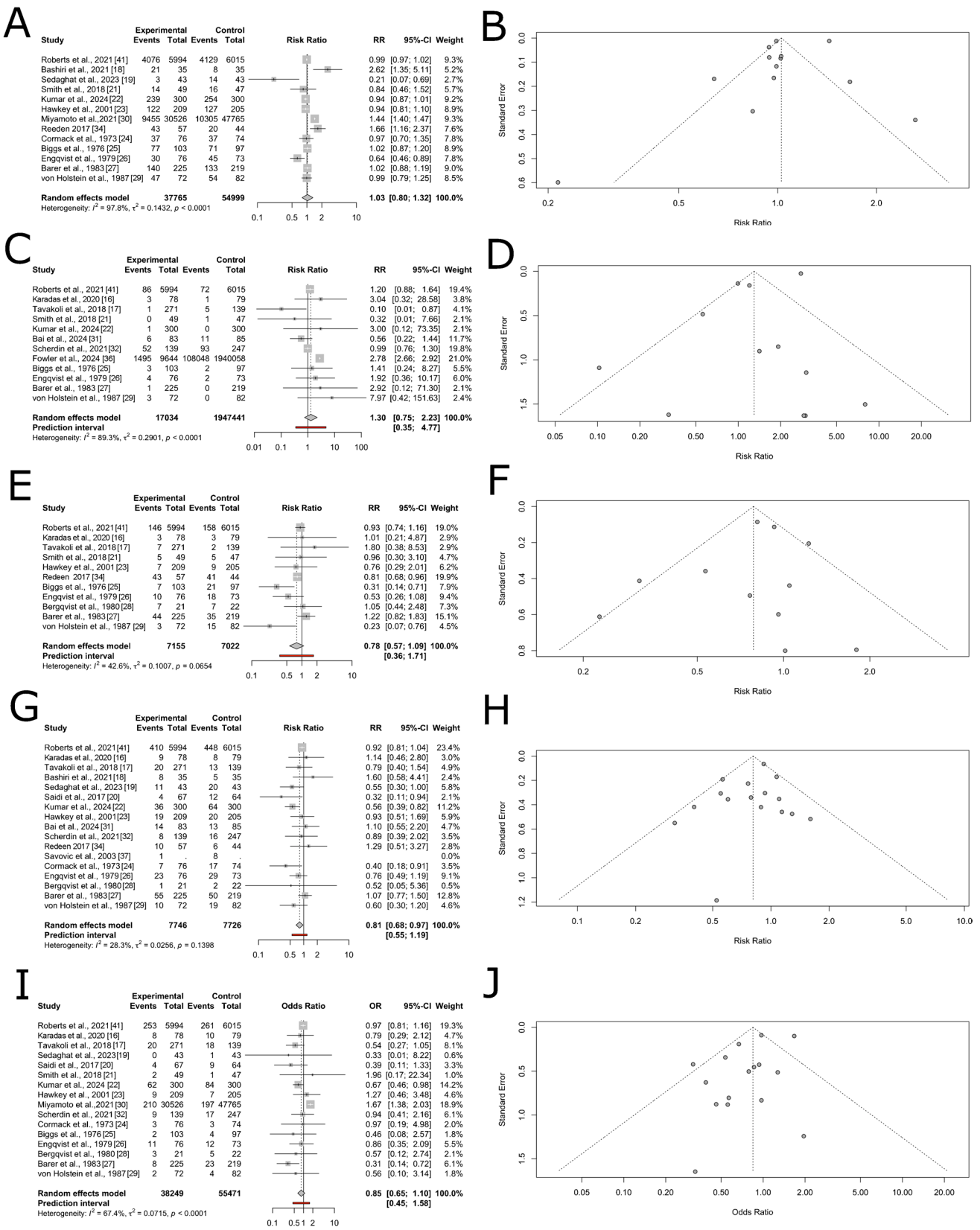


Fig. 3 **A** Transfusion rate analysis. **B** Funnel plot transfusion rate. **C** Thrombotic events thrombotic events. **D** Funnel plot thrombotic events. **E** Need for surgery analysis. **F** Funnel plot need for surgery. **G** Re-bleeding analysis. **H** Funnel plot re-bleeding. **I** Mortality analysis. **J** Funnel plot mortality

0.75 to 2.23, $p = 0.31$, I2= 89%) (Fig. 3C). The funnel plot showed asymmetry, but Egger's test ($p = 0.06$) did not indicate significant publication bias. The asymmetry may be due to heterogeneity or study design differences rather than bias (Fig. 3D).

Sub-group and sensitivity analysis

Sub-group analyses identified significant between-group differences for study year ($p = 0.01$), country ($p < 0.01$), type of bleeding ($p < 0.01$) and risk of bias ($p < 0.01$).

However, many significant findings were based on single-study sub-groups, limiting their reliability and increasing the risk of bias. For example, in the case of year and type of study sub-groups, meta-regression analysis was performed to assess the effect of publication year on the outcome and the test of moderators showed no significant association ($p = 0.48$). Studies with low risk of bias displayed the highest heterogeneity with no significant effect. Other sub-group analyses showed no significant differences, suggesting these factors did not modify the overall effect. Sensitivity analysis with leave-one-out analysis revealed Fowler et al., 2024 as an influencer of the overall result; the analysis excluding this article led to a still not significant result but with lower heterogeneity RR 1.04 (95% CI: 0.67 to 1.62, $p = 0.82$, I2=15) (Supplementary Tables 14 and 15).

Need for surgery

This analysis included 11 studies, comprising 14,177 participants (7155 in the TXA group and 7022 in the placebo group) and reported 596 patients requiring surgery. The random effects model yielded an RR of 0.78 (95% CI: 0.57 to 1.09, $p = 0.13$, I2= 42%) (Fig. 3E). The funnel plot showed asymmetry, but Egger's test ($p = 0.51$) did not indicate significant publication bias. The asymmetry may be due to heterogeneity or study design differences rather than bias (Fig. 3F).

Sub-group analysis and sensitivity analysis

Sub-group analyses identified significant between-group differences for study year ($p = 0.04$), risk of bias ($p = 0.03$) and route of administration ($p = 0.01$). However, many significant findings were based on single-study sub-groups, limiting their reliability and increasing the risk of bias. For example, in the case of year and type of study sub-groups, meta-regression analysis was performed to assess the effect of publication year on the outcome and the test of moderators showed no significant association ($p = 0.48$). Studies with some concerns on risk of bias displayed the highest heterogeneity, while the articles with low risk of bias displayed an RR of 0.85 (95% CI: 0.75 to 0.97, I2=0%), being significant to reduce the need for surgery. Other sub-group analyses showed no significant differences, suggesting these factors did not modify the overall effect. Sensitivity analysis with leave-one-out analysis reveals Biggs et al., 1976 as an influencer of the overall result. The analysis excluding this article led to a still not significant result but with lower heterogeneity RR 0.86 (95% CI: 0.68 to 1.10, $p = 0.21$, I2=22) (Supplementary Tables 16 and 17).

Re-bleeding

This analysis included 16 studies, comprising 15,472 participants (7746 in the TXA group and 7726 in the placebo group) and reported 1387 patients suffering from re-bleeding. The random effects model yielded an RR of 0.81 (95% CI: 0.68 to 0.97, $p = 0.02$, I2= 28%) (Fig. 3G). The funnel plot showed asymmetry, but Egger's test ($p = 0.24$) did not indicate significant publication bias. The asymmetry may be due to heterogeneity or study design differences rather than bias (Fig. 3H).

Sub-group and sensitivity analysis

Sub-group analyses identified significant between-group differences for dose per day ($p < 0.01$) and type of bleeding ($p < 0.01$). However, significant findings were based on single-study sub-groups, limiting their reliability and increasing the risk of bias in the dose per day. Studies with variceal and non-variceal bleeding patients showed the highest heterogeneity, but none of the groups reached significant results. Sensitivity analysis with leave-one-out analysis revealed Roberts et al., 2021 and Kumar et al., 2024 as influencers of the overall result; the analysis excluding these articles led to a non-significant result but without a significant decrease of the heterogeneity, RR 0.83 (95% CI: 0.67 to 1.03, $p = 0.07$, I2=13%) (Supplementary Tables 18 and 19).

Mortality

This analysis included 16 studies, comprising 93,720 participants (38249 in the TXA group and 55471 in the placebo group) and reported 1262 deaths. The random effects model yielded an RR of 0.85 (95% CI: 0.65 to 1.1, $p = 0.22$, I2= 67%) (Fig. 3I). The funnel plot showed asymmetry, but Egger's test ($p = 0.51$) did not indicate significant publication bias. The asymmetry may be due to heterogeneity or study design differences rather than bias (Fig. 3J).

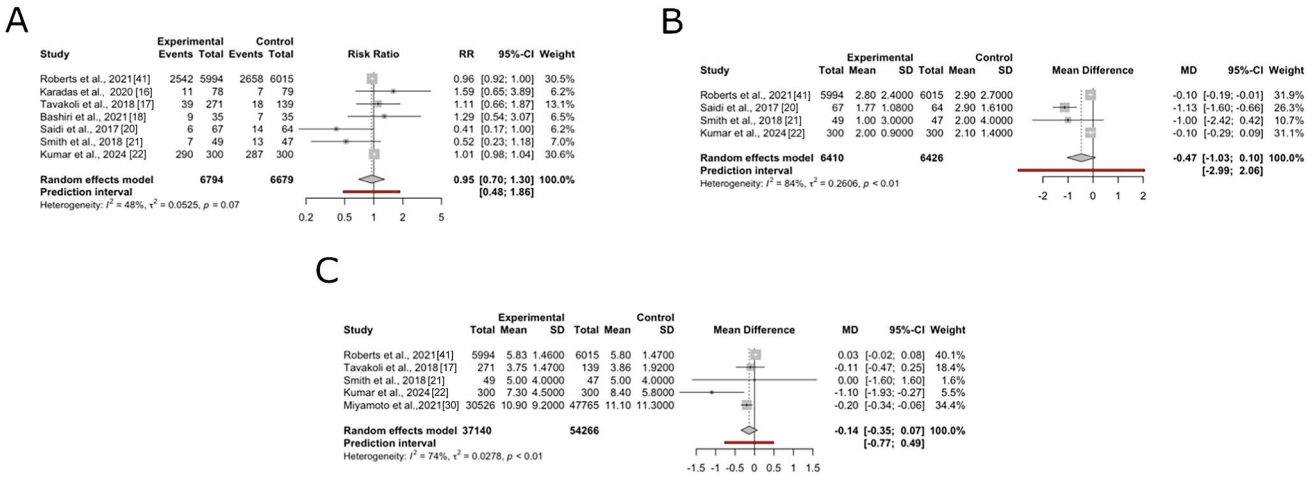


Fig. 4 **A** Analysis of need for endoscopy. **B** Analysis for transfusion volume. **C** Analysis for hospital length of stay

Sub-group analyses and sensitivity analyses

Sub-group analyses identified significant between-group differences for country ($p < 0.01$), dose per day ($p < 0.01$), administration route ($p < 0.01$), type of bleeding ($p < 0.01$), localization of bleeding ($p < 0.01$) and type of study ($p < 0.01$). Studies from Iran showed a significant effect RR 0.53 (95% CI: 0.34 to 0.81, I2=0%). Dose per day findings were based on single-study sub-groups, limiting their reliability. The administration for multiple routes showed a positive reduction of mortality with an RR: 0.56 (95% CI: 0.35 to 0,89, I2=0%); despite differences in type of bleeding and dose per day, none of the groups showed significance. For localization of bleeding, studies of upper GI bleeding showed an RR of 0.72 (95% CI: 0.59 to 0.87, I2= 0%), while studies of lower GI bleeding showed an RR of 1.67 (95% CI:1.44 to 1.93, I2= 0%). Analysis of the RCTs revealed a significant effect with an RR of 0.83 (95% CI; 0.70 to 0,97, I2=0%). Sensitivity analysis with leave-one-out analysis revealed Barer et al., 1983 as an influencer of the overall result; the analysis excluding this article led to a significant result with lower heterogeneity RR 0.87 (95% CI: 0.77 to 0.98, p =0.02, I2=0%) (Supplementary Tables 20 and 21).

Need for endoscopy

This analysis included seven studies, comprising 13,473 participants (6794 in the TXA group and 6679 in the placebo group) and reported 5908 patients requiring endoscopy. The random effects model yielded an RR of 0.95 (95% CI: 0.70 to 1.30, $p = 0.69$, I2= 48%) (Fig. 4A).

Sub-group and sensitivity analyses

Sub-group analyses identified significant between-group differences for study year ($p = 0.03$). However, significant findings were based on single-study sub-groups, limiting their reliability and increasing the risk of bias. For example, in the case of year and type of study sub-groups, meta-regression analysis was performed to assess the effect of publication year on the outcome and the test of moderators showed no significant association ($p = 0.36$). Other sub-group analyses showed no significant differences, suggesting these factors did not modify the overall effect. Sensitivity analysis with leave-one-out analysis revealed Saidi et al., 2017 as an influencer of the overall result; the analysis excluding this article led to a still not significant result but with lower heterogeneity RR 0.98 (95% CI: 0.92 to 1.05, p =0.63, I2=36) (Supplementary Tables 22 and 23).

Transfusion volume

This analysis included four studies comprising 12,836 participants (6410 in the TXA group and 6426 in the placebo group). The random effects model yielded an MD of −0.47 (95% CI: −1.03 to 0.1, $p = 0.1$, I2= 84%) (Fig. 4B).

Sub-group analyses and sensitivity analyses

Sub-group analyses identified significant between-group differences for the study year ($p = 0.03$). The meta-regression analysis showed that the year of publication was a significant moderator, explaining 63.01% of the heterogeneity ($p = 0.03$). For each additional year, the effect size increased by 0.15 units ($p = 0.03$). Despite this, significant residual heterogeneity remained ($p < 0.01$), suggesting other factors

may also contribute to the variability between studies. Other sub-group analyses showed no significant differences, suggesting these factors did not modify the overall effect. Sensitivity analysis with leave-one-out analysis revealed Saidi et al., 2017 as an influencer of the overall result; the analysis excluding this article led to a still not significant result, but with lower heterogeneity RR 0.98 (95% CI: 0.92 to 1.05, p =0.63, I2=36) (Supplementary Tables 24 and 25).

Hospital length of stay

This analysis included five studies comprising 91,406 participants (37,140 in the TXA group and 54,266 in the placebo group). The random effects model yielded an MD of −0.14 (95% CI: −0.35 to 0.07, $p = 0.19$, I2= 74%) (Fig. 4C).

Sub-group and sensitivity analysis

Sub-group analyses identified significant between-group differences for study year ($p < 0.01$), country (p <0.01), use of PPI (p =0.02), follow-up (p =0.02) and localization of bleeding (p <0.01). However, all significant findings were based on single-study sub-groups, limiting their reliability and increasing the risk of bias. Other sub-group analyses showed no significant differences, suggesting these factors did not modify the overall effect. Sensitivity analysis with leave-one-out analysis revealed Saidi et al., 2017 as an influencer of the overall result; the analysis excluding this article led to a still not significant result but with lower heterogeneity RR 0.98 (95% CI: 0.92 to 1.05, p =0.63, I2=36) (Supplemental Table 25 and 26).

Publication bias

The funnel plot and Egger's test analysis for the previous analysis were not feasible due to the limited number of studies.

Discussion

This SR and meta-analysis of 23 studies, including 15 RCTs and eight observational studies, with over two million participants, provides comprehensive evidence on using TXA in patients with acute GI bleeding. The qualitative synthesis indicates that 74% of the included studies saw improved results in at least one parameter with TXA use, such as bleeding, re-bleeding rates, mortality, need for endoscopy, surgery and blood transfusions. The remaining 26% saw either increased complications, no clinical benefit or no significant difference. Several studies (52%) reported adverse outcomes in the form of thrombotic events. Among them, 30.4% showed a higher rate of these events in the TXA group than the placebo, while 21.7% demonstrated more adverse events in the control group. Additionally, from the eight studies reporting the need for endoscopic intervention, the TXA group exhibited a reduced need for endoscopy in 50% of them.

In agreement with our qualitative synthesis findings, our meta-analysis demonstrated a clear benefit of TXA for reducing re-bleeding and mortality in UGIB, with multiple routes of administration and when only RCTs were included. The need for surgery was decreased in studies classed as a lower risk of bias. In contrast, there wasn't proof of a clear benefit in terms of transfusion rate or volume, hospital length of stay, need for endoscopy and hospital length of stay. Additionally, heterogeneity and potential biases within specific sub-groups limited the generalizability of some findings.

The results of this meta-analysis align with prior studies indicating the hemostatic effectiveness of TXA in various bleeding scenarios [17–20, 22, 30]. Our analysis further expands on these findings by demonstrating TXA's potential to decrease the re-bleeding events in GI bleeding cases [15, 17, 18, 21]. We found a statistically significant reduction in re-bleeding rates (RR 0.81, 95% CI: 0.68 to 0.97, $p = 0.02$), supporting TXA's role in managing GI bleeding. However, when excluding two large studies (Roberts et al., 2021 and Kumar et al., 2024) [7, 22], the re-bleeding effect became non-significant (RR 0.83, 95% CI: 0.67 to 1.03, $p = 0.07$), highlighting that these studies strongly influenced the overall result. Without these more extensive studies, the remaining smaller trials lacked the statistical power to maintain significance.

Another systematic review and individual patient data (IPD) meta-analysis reported similar findings to ours, indicating that TXA reduced bleeding, resulting in a statistically 20% reduction in the odds of death within three hours of bleeding onset. Additionally, they found no significant increase in the risk of vaso-occlusive events [8]. On the other hand and in contrast to our findings, other authors have reported no statistically significant variance in mortality between the administration of TXA and placebo. Furthermore, they found no discernible differences between the two groups in re-bleeding, transfusion requirements, the need for surgery and endoscopy and the risk of thromboembolism [38]. A comprehensive Cochrane systematic review, which included eight RCTs, found no significant difference between the use of TXA and control interventions regarding the risk of thromboembolic events. The analysis also indicated no variance in transfusion assessment between the groups and no discernible positive or negative effects of TXA compared to anti-ulcer medications [39].

Overall, we found that TXA is not effective in reducing the need of surgery, aligning with the findings of previous analyses by Lee (2021) and O'Donnell (2024) [38, 40]. Nevertheless, when low-risk of bias articles were analyzed, we

found a decrease in the need for surgery for TXA patients with null heterogeneity compared to previous studies published. This raises the need for better-quality RCTs to evaluate the effect of TXA in reducing the need for surgery.

For mortality outcomes, we found an RR of 0.85 (95% CI: 0.65 to 1.1, $p = 0.22$, I2= 67%), similar to previously published results reporting an RR of 0.86 (95% CI: 0.74 to 1.0, I2=0%) for O'Donnel et al. 2024 [38] and an RR of 0.6 (95% CI: 0.45 to 0.8) reported by Lee et al. 2021 [40]. Our findings add to those of the authors mentioned above in the subgroups and sensitivity analyses performed. Another unique feature of our research was to take the mortality numbers of the HALT-IT trial at 28 days after the intervention instead of the values of five days post-intervention. This allowed us to increase standardization within our sub-group analysis among included articles.

Regardless, we found statistically significant differences in mortality when performing the sub-group analysis, showing that mortality UGIB showed a lower risk RR = 0.72 (95% CI: 0.59 to 0.87, I2= 0%). The same findings were reported by a previous Cochrane meta-analysis that showed that UGIB is reduced with TXA showing an RR of 0.6 (95% CI:0.42 to 0.87) and similar results by O'Donnell et al. reporting an RR of 0.85 (95% CI: 0.72 to 0.99) [38, 39]. Our analysis allowed the reduction of the CI and shed light on the LGIB effect of TXA, evidencing that for this population, there is an increased risk of mortality in LGIB with a RR 1.67 (95% CI:1.44 to 1.93, I2= 0%). In addition, our findings elucidate that the route of administration effects mortality, with the sub-group of multiple routes in the same patient demonstrating a positive reduction in mortality. When analyzing RCTs alone, the effect is significant and the heterogeneity decreases to zero, providing credibility to the findings of the sub-group analysis.

The current analyses did not reveal any significant differences in the benefits of TXA for variceal, non-variceal or mixed bleeding populations. This contrasts with earlier reports that suggested TXA was effective in reducing mortality, with a reported RR of 0.75 (95% CI: 0.6–0.94, $I^2 = 0\%$) [8]. These discrepancies can be attributed to the unclear classification of variceal and non-variceal bleeding in previous studies. For example, studies such as Cornmack et al., 1973 [24], did not specify whether patients had variceal or non-variceal bleeding, leading to misclassification. Even in more recent studies, such as the HALT-IT trial (2021), which was classified as "non-variceal," over 40% of the patients were suspected of having had variceal bleeding [41]. These classification issues introduced bias into the results, which our analysis addressed through more accurate sub-group classification.

The findings of this study have important implications for managing GI bleeding. By thoroughly examining the available evidence, we have clarified the benefits and risks of TXA, offering valuable insights for clinical decision-making and future research. Our results provide new, robust evidence that TXA significantly reduces mortality in UGIB when administered through multiple routes, especially when the influential Barer et al. study was excluded. Additionally, the need for surgery decreased when high-risk-of-bias studies were removed from the analysis. While TXA showed evidence of reducing re-bleeding rates overall, the effect became non-significant when two influential studies were excluded, likely due to limited sample size. However, clinicians should carefully assess the benefits and risks of TXA for each patient and perform monitoring, considering individual thrombotic risk profiles and the severity of the bleeding. The discrepancy in results with previous analyses and the statistical significance of some variables in our meta-analysis add to the need for further and more consistent research protocols to elucidate the benefits and risks of TXA as a treatment for GI bleeding.

Strengths and limitations

The meta-analysis has several notable strengths, including a comprehensive search strategy, RCTs and observational studies and a large sample size. In our comprehensive assessment, we reviewed a significant number of recent studies, analyzing eight distinct variables through subgroup and sensitivity analyses. These features surpass previous research on appraising the efficacy of TXA as a treatment for acute GI bleeding, bridging the knowledge gap regarding the potential use of this treatment as an adjunctive option. Furthermore, the study was conducted through risk of bias assessments using appropriate tools. Among the study's limitations is the PRISMA chart, which reveals a search limited to English and Spanish, potentially excluding relevant studies in other languages. Access issues such as the inability to retrieve specific full-text articles, may have impacted the breadth of the review. These limitations should be considered when interpreting the findings.

To conclude, this systematic review and meta-analysis comprehensively evaluated the efficacy and safety of TXA in managing acute GI bleeding. Our findings suggest that TXA significantly reduces re-bleeding in patients, particularly in UGIB. However, the reduction in re-bleeding became non-significant when two large studies were excluded, indicating that these larger trials strongly drove the overall result. When only RCTs were analyzed, a significant reduction in mortality was observed, highlighting the potential benefit of TXA in this patient population. This effect was particularly evident when multiple routes of administration were used and in UGIB, while TXA may increase the risk of mortality in LGIB. These findings highlight the importance of careful patient selection and monitoring and the need for high-quality RCTs to further validate the efficacy and safety of TXA, particularly in different types of bleeding.

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Data availability All data used for this analysis is publicly available in the referenced articles. The remaining material is at the author's discretion upon reasonable request.

Declarations

Competing interests ECM, GDBS, CSC, NAW, YS, DSD, MKG, SC, FMCC, RSM, RBB, AM and RA declare no competing interests.

Ethics approval and consent to participate This meta-analysis utilized previously published data from studies that had already obtained ethical approval and consent to participate, so no additional ethical approval or consent was required for this research.

Consent for publication All authors have provided their consent for publication.

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